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REVIEW

Periostin in cardiovascular disease and development: a tale of two distinct roles

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Abstract Tissue development and homeostasis are dependent upon the concerted synthesis, maintenance, and degradation of extracellular matrix (ECM) molecules. Cardiac fibrosis is now recognized as a primary contributor to incidence of heart failure, particularly heart failure with preserved ejection fraction, wherein cardiac filling in diastole is compromised. Periostin is a cell-associated protein involved in cell fate determination, proliferation, tumorigenesis, and inflammatory responses. As a non-structural component of the ECM, secreted 90 kDa periostin is emerging as an important matricellular factor in cardiac mesenchymal tissue development. In addition, periostin's role as a mediator in cell–matrix crosstalk has also garnered attention for its association with fibroproliferative diseases in the myocardium, and for its association with TGF-β/BMP signaling. This review summarizes the phylogenetic history of periostin, its role in cardiac development, and the major signaling pathways influencing its expression in cardiovascular pathology. Further, we provide a synthesis of the current literature to distinguish the multiple roles of periostin in cardiac health, development and disease. As periostin may be targeted for therapeutic treatment of cardiac fibrosis, these insights may shed light on the putative timing for application of periostin-specific therapies.

Keywords Periostin · Extracellular matrix · Cardiac fibrosis · Myocardial infarction · Cardiac fibroblasts · Cardiac development

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Introduction

Tissue development and homeostasis are dependent upon the concerted synthesis, maintenance, and degradation of extracellular matrix (ECM) molecules. The ECM is composed of a dynamic organizational and signaling network which governs the functional needs of tissue and how it responds to various stimuli. Fundamental cellular processes are regulated by matricellular proteins including cell-associated proteins, intercellular matrikines, enzymatic cleavage products and matricryptins, and structural factors within the ECM. In recent years, much attention has been directed towards periostin, a cell-associated protein involved in cell fate determination, proliferation, tumorigenesis, and inflammatory response. Initially identified as the bone-specific adhesion molecule osteoblast-specific factor 2 (OSF-2) [100], periostin has since been recognized a player in the ECM response in various tissue pathologies including muscle and vascular injuries [8, 48, 58, 83, 85, 91–93, 108]. Periostin is known to be important in cardiac development and its role as a regulator or indicator of pathologies involving the cardiovascular system is an emerging area of interest. A wealth of evidence has indicated the prominent role of periostin in coronary artery disease (CAD) and hypertension [45, 56, 61,

65, 108], valvular disease [21, 50, 71] and various etiologies of cardiac fibrosis [110, 116, 117].

Emerging evidence suggests that periostin is a novel therapeutic target in cardiovascular disease. Signaling pathways regulating cardiac periostin expression are pleiotropic and often coupled to cytoskeletal dynamics and extracellular stimuli. New insights into the expression of periostin in the remodeling myocardium indicate that it is specific to activated myofibroblasts, the primary contributors to cardiac fibrosis. Herein, we summarize the phylogenetic history of periostin, its role in cardiac development, and the major signaling pathways influencing its expression in various cardiovascular pathologies. As periostin may be targeted for therapeutic treatment of cardiac fibrosis, these insights may shed light on the putative timing for application of periostin-specific therapies.

Periostin and the FAS1 domain superfamily

Background

Periostin was first recognized as an essential player in osteoblast differentiation and response to transforming growth factor-β (TGF-β) signaling [39, 100]. At approximately 90 kDa, periostin is classified as a cell-associated, or matricellular, glycoprotein as it does not contain a transmembrane domain and is expressed as a non-structural protein in the ECM. Rather, periostin exhibits significant structural homology to fasciclin I, an adhesion molecule described in insect developmental studies in *D. melanogaster* [12, 28, 86] and *Schistocerca americana* [9]. Fasciclin (FAS1) domains comprise a relatively conserved sequence of 150 amino acids found in many membrane-bound and secreted proteins across all phyla, and are often observed as scattered repeats or in tandem among other domains [20, 67]. Periostin is especially like fasciclin I because both proteins contain FAS1 domains in four consecutive, tandem repeats (Fig. 1). Other notable members of the fasciclin superfamily bearing a similar structure and function include: periostin-like factor (PLF) [64, 66] and transforming growth factor-β-induced

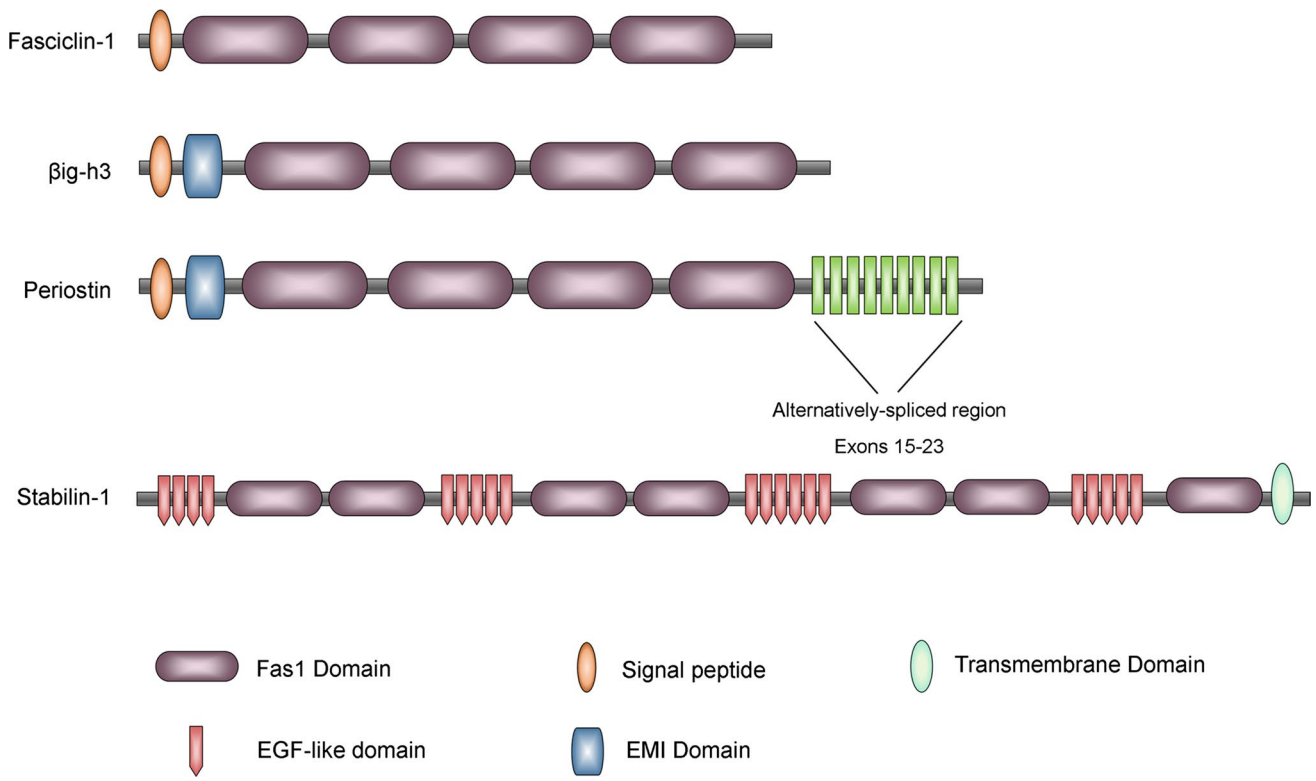

Fig. 1 A comparison of periostin and the other members of the FAS1 Domain superfamily of proteins. Human periostin is expressed as a 90 kDa protein with an alternatively spliced region consisting of nine exons at the C-terminus, and four consecutive FAS1 domains in the central portion of the protein. The EMILIN (EMI) domain at the N-terminus is believed to serve as a site for multimer formation. Unlike the other members of the FAS1 family of proteins, Stabilin-1 also contains several epidermal growth factor (EGF)-like domains, which are typically associated with membrane-bound proteins

protein IG-H3 (βIG-H3) [65–67, 95]. While the exact function of FAS1 domains remains elusive, evidence suggests that they may serve as a self-dimerization interface which modulates the strength of ligand-binding [75], or mediate protein–protein interaction [66]. Other members of the fasciclin superfamily, such as stabilin I and II, contain transmembrane domains and act as cell-surface scavenger receptors for many ECM components, such as hyaluronan and glycoproteins [89].

Another important structural feature present in periostin and βIG-H3 is the N-terminal EMI domain, a highly conserved cysteine-rich domain originally discovered in the Emilin family of proteins [26, 80]. Functional studies in *C. elegans* and other metazoans suggest that extracellular EMI domains serve as sites for protein–protein interaction, as hydrophobic pockets can form between the first and fourth cysteine residues [16]. A study in corneal dystrophy showed that the EMI domain allows periostin to heterodimerize with βIG-H3, facilitating is secretion from human corneal fibroblasts [49]. Although this interaction has yet to be examined in the heart, some have suggested that it might serve as an important regulator of TGF-β signaling, as other EMI domain-containing proteins have been shown to inhibit TGF-β signaling pathway components [80].

Despite being relatively conserved across phyla, the 23 exons of human periostin can be alternatively spliced to form seven possible splice variants [7, 33, 76, 100, 102]. While the physiological functions of each encoded isoform have yet to be fully elucidated, pathological functionality, ranging from cancer metastasis to cardiac fibrosis and remodeling, has been attributed to splice variants containing exons 17 and 21 [7, 102]. Although this may be the case for soft tissue, the full-length mRNA of periostin is essential in bone formation, resorption and fracture healing [13, 41]. Periostin evidently plays a vital role in the activation and progression of fibro-proliferative pathologies, and understanding its functional and signaling properties is critical to advancing our understanding of cell–matrix interactions in health and disease.

Expression of periostin and signaling crosstalk in the heart

As a potent modulator of cell–matrix interaction, periostin has been implicated in crosstalk between multiple signaling pathways which regulate cell migration, adhesion, and proliferation (Fig. 2). Despite this, very little is known regarding the transcriptional regulation of periostin. The most studied pathways associated with periostin expression are of the TGF-β superfamily in mesenchymal cells, which has established periostin as a focal contributor to collagen fibrillogenesis in response to injury and inflammation [5, 51, 78, 96, 107]. Early in vitro studies demonstrated that exogenous treatment of primary cardiac fibroblasts and vascular smooth muscle cells (VSMCs) with recombinant TGF-β1 promoted the expression of periostin *via* canonical SMAD-dependent signaling [56, 70, 96, 97]. Similar studies in embryonic chick atrial cushions confirmed that periostin is positively regulated by TGF-β3 [82]. Immunological studies have also linked inflammation and immune response to the TGF-β/periostin axis of signaling in fibrotic heart disease and idiopathic dilated cardiomyopathy [4, 17]. Conversely, the induction of periostin by TGF-β1 is markedly hindered by the use of anti-TGF-β antibodies [42] as well as dominant-negative mutant TGF-β Receptor type II (TGF-βRII) [18], suggesting that not only is the periostin promoter TGF-β-responsive, but also that latent TGF-β may assist in mediating periostin signaling in cardiac tissues.

Besides being induced by canonical TGF-β signaling, periostin promotes collagen fibrillogenesis by supporting bone morphogenic protein-1 (BMP-1) in mediating the activation of matricellular lysyl oxidase (LOX) [31, 73]. Specifically, secreted periostin sequesters BMP-1 and increases its deposition on fibronectin-rich ECM; this promotes the proteolytic activation of pro-LOX and collagen cross-linking [73]. Snider et al. utilized a periostin$^{-/-}$ mouse model to show that periostin knockout mice were susceptible to disorganized matrix stratification, reduced transforming growth factor signaling, misexpress the proteoglycan aggrecan (commonly found in cartilage), valve leaflet discontinuity and delamination defects [96]. The absence of a functional inhibitory SMAD6 produced a Marfan-like syndrome characterized by aortic stenosis and, occasionally, a bicuspid aortic valve [101]; speculating as to the putative connection of this SMAD to periostin, reduced subsequent bioavailability of periostin and subsequent inhibition of cell fate determination. In addition, parallel studies regarding atrioventricular valvulogenesis have linked periostin promoter activation to BMP-2 overexpression [31, 44], strengthening the causal link between periostin expression and signaling within the TGF-β superfamily. Although there exist much data to substantiate the TGF-β/BMP-periostin signaling axis, further studies are needed to identify the regulatory components that govern periostin transcription.

Apart from being expressed in response to SMAD-dependent TGF-β signaling, periostin activates a multitude of intracellular signaling pathways via its interaction with cell-surface receptors and in response to mechanical stress. Periostin-associated ECM components including: fibronectin and tenascin-C (TNC) [48], and collagens type I, III and V [27, 78, 99], are responsible for governing the biomechanical properties of tissues, ergo periostin-associated regulation of these components may help to determine tissue biomechanics. Special interest has been taken regarding TNC, as it directly associates with periostin FAS1 domains to organize fibronectin–collagen ECM structure [48], and is

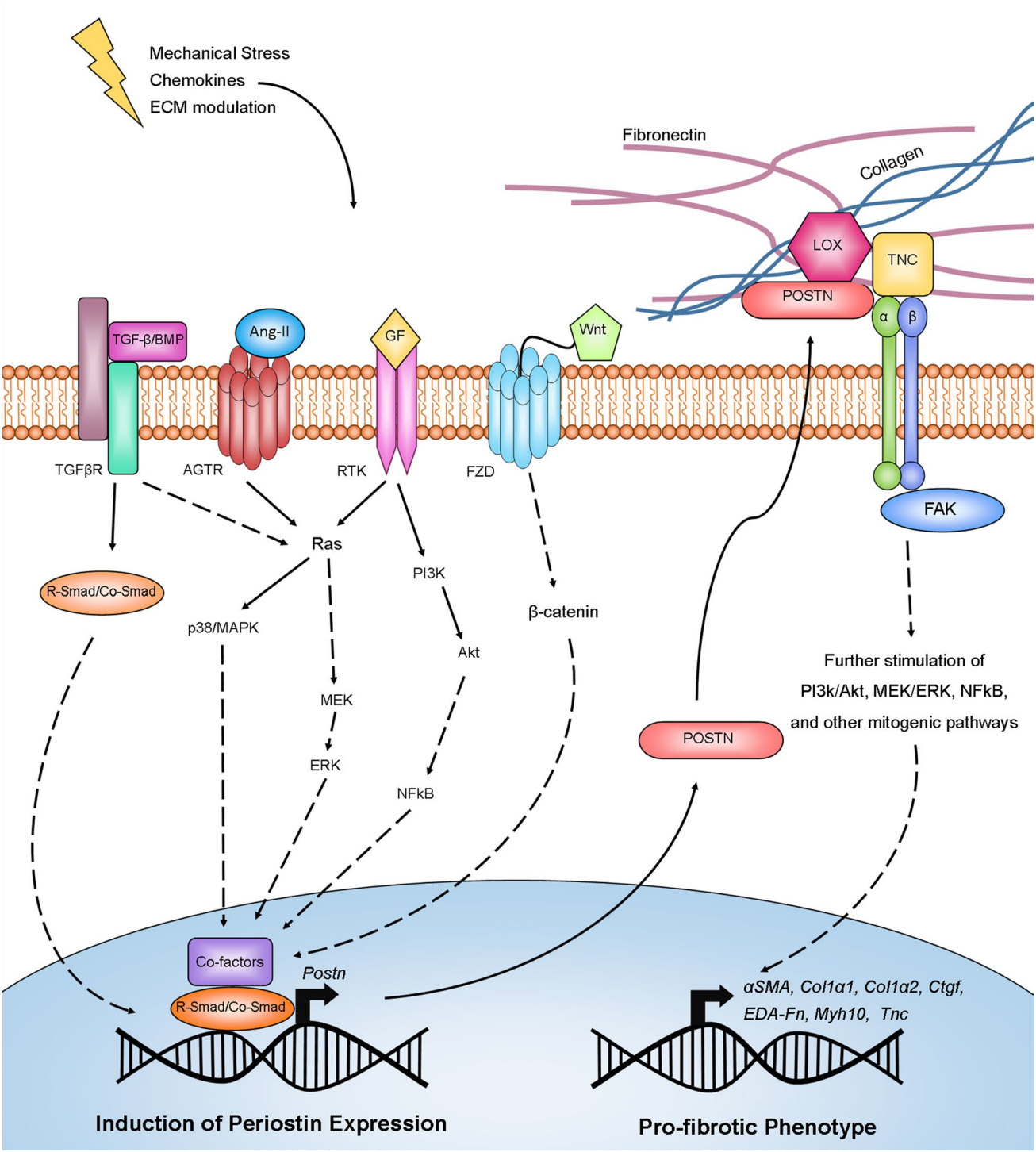

Fig. 2 The major signaling pathways involved in periostin expression and function in cardiac cells of mesenchymal origin. Mechanical stress, chemokines and changes in matrix composition trigger signaling pathways which induce Smad-dependent periostin (POSTN) expression and subsequent secretion. In turn, periostin interacts with matrix-associated lysyl oxidase (LOX) and tenascin-C (TNC), stimulating mitogenic $\alpha_v\beta_1$, β_3, and β_5 integrin signaling. In turn, a pro-fibrotic phenotype is further established in a feed-forward signaling cascade. *Akt* RAC-alpha serine/threonine-protein kinase, *α-SMA* alpha-smooth muscle actin, *Ang*-II angiotensin-II, *AGTR* angiotensin-II receptor, *BMP* bone morphogenic protein, *Col1α1/2* collagen type I, alpha 1 and 2, *Ctgf* connective tissue growth factor, *EDA-Fn* EDA-containing cellular fibronectin, *ERK* extracellular signal-regulated kinases, *FAK* focal adhesion kinase, *FZD* frizzled, *GF* growth factor, *MAPK* mitogen-activated protein kinase, *MEK* mitogen-activated protein kinase kinase, *Myh10* myosin heavy chain 10 or non-muscle myosin IIB, *NFκB* nuclear factor kappa light-chain enhancer of activated B cells, *TGF-β* transforming growth factor-β

also activated by mechanical stress in cardiovascular pathologies [43, 114]. It has been reported that periostin stimulates cell migration and invasion through biomechanically and biochemically sensitive integrin communication. Various reports attribute periostin-mediated cancer cell proliferation to Arg-Gly-Asp (RGD) matricryptin-associated αvβ1, β3 and β5 integrin signaling [33, 90, 104]. Similar studies in cardiovascular cells of mesenchymal lineage indicate that periostin facilitates vascular and valvular cell migration and hyperplasia via the same set of integrin receptors [15, 32, 55]. Within the cell, the cytoplasmic domains of integrin complexes trigger a gamut of mitogenic signaling cascades. Not surprisingly, cardiovascular periostin expression has been shown to activate integrin-associated p38/MAPK [57], FAK and PI3K/AKT [19, 55] and WNT/β-Catenin [2] signaling cascades in fibroblasts and VSMCs during cardiac development and disease. Finally, it has been shown in various pathologies that latent TGF-β associated with αv integrin subunits is released upon stimulation by mechanical stress [3, 37, 47, 109]. Cell contraction or a change in ECM composition leading to the release of latent TGF-β might leave integrins open to interaction with periostin, triggering a feed-forward loop of periostin signaling. While this has yet to be examined in the heart, the TGF-β–integrin–periostin relationship could better our understanding of fibrogenic cardiovascular diseases and provide a novel target for therapeutic intervention.

Periostin in cardiac development—valve maturation and the mesenchyme

Early murine studies in the role of periostin in cardiac development were prompted by the discovery of its role in the remodeling myocardium, post-MI [50, 98]. Endocardial cushions from embryonic day (E) 10.5 express low levels of periostin mRNA, which increases markedly from E12.0 forward [50]. The same report also demonstrated that periostin expression was excluded from cardiomyocytes, as it was primarily detected in the endocardial cushion, and that it promotes dose-dependent cell migration and proliferation during valve maturation [15]. This notion was robustly substantiated by subsequent reports which determined that periostin is expressed by cells of mesenchymal lineage, such as those responsible for the formation of the chordae tendineae and valvular septum [62, 78, 79]. Further studies in a cardiac-specific periostin reporter mouse model concluded that periostin was solely expressed by non-cardiomyocytes, and plays an integral role in the morphogenesis of valve leaflets and the cardiac fibrous scaffold during embryogenesis [96].

Periostin also appeared to be prominently expressed by differentiating VSMCs and cardiac fibroblasts during valvulogenesis [78, 79]. Periostin null mice exhibited a modest degree of embryonic lethality due to the appearance of MF20-positive cardiomyocyte progenitor cells in the atrioventricular cushion, suggesting aberrant signaling for myocardial differentiation [81]. The surviving null mice exhibited truncated valve leaflets and ectopically developed smooth muscle. It was also determined that lack of cardiac periostin resulted in insufficient fibrillar collagen deposition and maturation during valvulogenesis, with abnormal encroachment of myocardium along the ventricular leaflet of the tricuspid valve [81, 82]; this suggests that periostin expression assists in restricting the boundaries between tissue types during cardiac development. Norris et al. also concluded from their extensive studies regarding valvulogenesis that periostin is also required for the commitment of mesenchymal progenitors to the cardiac fibroblast phenotype [80, 82]. Periostin is a vital component to the maturation and montage of the tissues of the heart, and provides the necessary signaling for the proper formation of the three-dimensional cardiac collagen scaffold during cardiac morphogenesis.

The role of periostin in cardiovascular disease

Hypertension and vasculopathies

The conversion of VSMCs into a hyperproliferative, hypersecretory phenotype is a hallmark of the vascular response to injury. Neointimal formation due to excessive ECM deposition has been linked to increased expression of several periostin splice variants, which facilitate the migration and proliferation of VSMCs [55, 61, 65]. Wang et al. demonstrated in an atrial natriuretic peptide (ANP) null mouse pressure overload model that periostin expression is increased in the myocardial interstitial and coronary arteries [108]. The study also indicated that ANP negatively regulates periostin expression, as the null mouse showed marked overexpression of periostin by VSMCs and cardiac fibroblasts after transverse aortic constriction (TAC). Similar studies in a rat model of pulmonary hypertension also confirmed the inhibitory effects of ANP on TGF-β-mediated periostin expression in pulmonary arterial smooth muscle cells [59]. Subsequent studies in a rat carotid balloon injury model indicated there is a spatiotemporal pattern to the expression of periostin following the initial insult [56]. At 1 week post-injury, periostin expression was prominently expressed in the medial VSMCs of the injured artery, while the uninjured vessels showed minimal expression. Between 2 weeks and 1 month after injury, the neointima presented an abundance of periostin, suggesting that it has functional importance in the initiation and progression of atherosclerosis and restenosis after percutaneous coronary intervention [56].

As a major contributor to many etiologies of hypertension, and a mediator of ECM deposition, Angiotensin-II (ANG-II) is also a driving factor which regulates pathological periostin expression. Using a chronic ANG-II infusion rat model of hypertension, Li et al. observed increased periostin expression within the myocardial interstitium compared to untreated animals, and these effects were revealed to be mediated by p38/MAPK signaling [57]. Similar effects were observed in isolated cardiac fibroblasts treated with Ang-II, in vitro. However, the effects of ANG-II on periostin expression within vascular walls and the myocardium have been reduced by introducing commonly prescribed ANG-II receptor blockers such as losartan [57] and valsartan [34]. Concurrent studies in a high salt-induced hypertension in vivo model further strengthened the case for periostin as a central mediator of pressure overload vasculopathy, and even implicate it as a contributor to oxidative stress in hypertension [110]. Finally, a recent study conducted by Ling et al. on a group of 50 patients diagnosed with ST-elevation myocardial infarction (STEMI) showed that serum periostin levels were negatively correlated with left ventricular function, and left anterior descending coronary artery restenosis in the 6 months following clinical intervention [63]. Although this was a small study, the evidence strongly suggests that periostin could serve as a prognostic marker for short-term management of patients who have undergone recent coronary revascularization, post-myocardial infarction (post-MI).

Valvular disease

The cardiac valve leaflet is composed of three distinct layers of ECM components, each serving a different function to mitigate the effects of the tremendous biomechanical forces endured during the cardiac cycle [38]. The heterogeneous nature of the resident valve leaflet cell population makes it susceptible to malfunction if any disturbance in their distribution and phenotype occurs. Several genetic connective tissue disorders originating from mutation in ECM proteins have been associated with aberrant cardiac valve maturation and function, and this feature is often linked to anomalous periostin expression [25, 32, 80, 96]. Valvular interstitial cells (VICs) are the most abundant cell type within the leaflet, and result from the endothelial–mesenchymal transition of cells within the endocardial cushion during cardiac development [54]. Using a murine model of a heterozygous *Fibrillin-1* mutation to mimic Marfan syndrome, Horne et al. demonstrated that periostin expression is markedly increased by VICs in all layers of the mitral valve, compared to wild-type mice [40]. The same group examined myxomatous mitral valve biopsies from male patients undergoing reparative surgery and observed a significant increase in periostin in the ventricularis, with minimal detection within the fibrosa and spongiosa, noting that periostin-positive mesenchymal cells were not necessarily also staining positive for the fibrotic myofibroblast marker, α-smooth muscle actin (α-SMA) [40]. Other groups have reported that periostin is expressed in both surface layers of healthy human valve leaflets, with more pronounced expression in the aortic ventricularis and mitral fibrosa [35].

Apart from its role in congenital valve defects, periostin also stimulates the progression of degenerative valve diseases. Work by Lorts et al. demonstrates that periostin expression is greatly increased in the vasculature and valves of patients with stenotic and rheumatic valve disease [69]. Subsequent investigations confirmed these findings regarding aortic stenosis, and revealed that periostin over-expression in the valve leaflet leads to increased secretion of matrix metalloproteinase-2 (MMP-2) and MMP-9, resulting in tissue remodeling and calcification [36, 103]. Hakuno et al. compared wild-type mice to a novel *Periostin*$^{-/-}$ mouse line for valve thickening and degeneration induced by a high-fat (HF) diet revealed that the contributing role of periostin is marked, as M-mode echocardiography of wild-type mice revealed significant aortic valve remodeling while the periostin null mice were protected [36]. These authors conclude that periostin is directly involved with HF diet-induced degeneration of aortic valves. Recent proteomics analyses also support the notion of periostin as a potential biomarker to identify both male and female patients at risk of developing degenerative aortic stenosis [72]. These data corroborate previously published evidence which indicated that periostin expression is increased in the aortic valve and left ventricle (LV) of both male and female patients undergoing stenotic valve replacement surgery, although multiple studies report higher serum concentrations of periostin in males than females [74, 88]. Regardless of the etiology of cardiac valvular dysfunction, periostin is upregulated during valvular disease in response to the need for increased ECM, and invokes a fetal gene program seen in fibrotic pathologies.

Cardiac fibrosis

Nearly, all forms of heart disease and heart failure are associated with cardiac fibrosis, a condition defined by the abnormal thickening of the myocardium due to the excessive deposition of ECM components by activated cardiac fibroblasts. While some fibrosis must heal damaged tissue, the expansion of cardiac ECM leads to the loss of proper ventricular architecture, electrical coupling, and contractility, ultimately resulting in heart failure.

As a chronic disease affecting a significant portion of the population in the developed world, diabetes mellitus (DM) is a primary determinant of cardiovascular pathologies [30]. Diabetic cardiomyopathy is typified by early onset of diastolic dysfunction independent of the presence of vascular disease, as oxidative stress and circulating advanced

glycation end-products contribute to the development of interstitial fibrosis [30, 111]. Investigations which used a streptozotocin-induced type 1 diabetes rat model showed that diabetic rat hearts expressed high levels of periostin mRNA and protein, relative to healthy controls [34]. It was also found that treating diabetic animals with valsartan reduced the expression of periostin, and collagen I and III [34]. Further studies on the role of periostin in diabetic cardiomyopathy found it may be overexpressed in DM in response to the chronic accumulation of reactive oxygen species in the myocardium [111]. Treatment of diabetic animals with the antioxidant resveratrol resulted in a significant reduction in myofibroblast activation, and inhibited the expression of periostin via ERK/TGF-β signaling [111]. Taken together, the evidence suggests that periostin functions as an intermediary in the initiation and progression of diabetic cardiomyopathy. While blocking its effects may assist in mitigating the effects of DM on the heart, further studies are required to fully understand the role of periostin in the diabetic heart.

Along with its effects on ventricular fibrosis, periostin has also been associated with atrial fibrosis, a pathology commonly attended by atrial fibrillation (AF) [113]. Much like ventricular fibrosis, TGF-β is often viewed as the primary mediator of atrial fibrosis [14, 17]. Thus, as a target of TGF-β signaling, periostin is likely to play a role in atrial fibrogenesis. A recent examination of atrial appendages from AF patients undergoing elective valve replacement surgery indicated a strong positive correlation between periostin expression and the extent of atrial fibrosis [112]. While these data do not procure a causal link between periostin, atrial fibrosis, and AF, the study also suggests that increased periostin levels in atrial tissues are associated with worsening heart failure and decreasing ejection fraction. Concurrent studies in a rabbit model of AF by Yuan et al. demonstrated that the expression of periostin in cardiac atria can be regulated by miR-30a, a miRNA associated with both cardiac and pulmonary fibrosis [115]. It was specifically shown that overexpression of miR-30a led to a decrease in periostin and atrial fibrosis. Conversely, inhibition of miR-30a promoted the expression of periostin in atrial tissue. Once again, while this potential axis of signaling is not fully understood, their findings further support the notion that periostin plays a role in the pathogenesis of cardiac fibrosis. Additional studies are still required to fully clarify whether periostin is triggering chronic fibrinogenesis or reinforces established feedback mechanisms which promote aberrant ECM deposition.

Post-MI cardiac remodeling

In contrast to chronic cardiomyopathies, cardiomyocyte death due to ischemia following MI results in the infiltration of macrophages and lymphocytes in response to the injury. Cardiac fibroblasts are then activated by TGF-β1 and mechanical stressors, leading to the deposition of ECM proteins and formation of a fibrotic scar. In the regions distal to the expanding infarct, reactive interstitial fibrosis is also observed in both left and right ventricles. Replacement fibrosis post-MI is thought to be essential to prevent cardiac rupture, as the collagenous scar possesses significant tensile strength, whereas continuous interstitial fibrosis and cardiac remodeling leads to progressive cardiomyocyte hypertrophy, chamber dilation, ventricular wall thinning, and overall loss of cardiac function and output.

The role of periostin in the post-MI heart has been primarily examined in the context of LV remodeling. Preliminary studies by Oka et al. in a mouse model of post-MI remodeling indicated that periostin is necessary for the proper formation of the infarct scar, as periostin$^{-/-}$ animals were susceptible to ventricular rupture within the first 2 weeks after MI [84]. Conversely, the group's periostin-overexpressing mouse line did not experience post-MI rupture; however, they developed spontaneous cardiac fibrosis and hypertrophy with age. When subject to TAC-induced pressure overload, the mice lacking periostin did not develop overt interstitial cardiac fibrosis or remodeling, as seen in wild-type animals [84]. These findings were later confirmed, as adenovirus-mediated rescue of *Postn*$^{-/-}$ infarcted myocardium protected post-MI hearts from ventricular rupture [94]. Subsequent studies by Shimazaki et al. in human tissue specimens confirmed that periostin is not expressed in healthy myocardium, and it strongly induced in ischemic and reperfused tissue [94]. In an in vivo mouse model of post-MI remodeling, the same group confirmed that periostin deletion prevented stiffening of the LV free wall and attenuated chamber dilatation; however, it should be noted that there was an overall decrease in the number of vimentin-positive (mesenchymal) cells within and surrounding the infarct. Furthermore, it was found that periostin ablation resulted in a decrease in FAK activation, which may account for the decrease in myofibroblast migration [94] into the infarcted area. These findings postulate that periostin may be required to initiate the invasion of infarcted tissue by activated myofibroblasts during post-MI wound healing. Despite these studies, it was still unclear which mesenchymal cells handled periostin-mediated post-MI cardiac remodeling. Further reports by Molkentin's group showed in lineage tracing analyses in mice that TCF21^{+} resident cardiac fibroblasts are the overwhelming majority of periostin-expressing cells within and surrounding the infarct scar [46]; this is in sharp contrast to previous investigations which suggested that activated cardiac fibroblasts originate from multiple sources [1, 6, 105]. Thus, it is evident that periostin likely plays a key role in regulating fibroblast function, and mediates the myocardium's response to injury.

Given the growing evidence suggesting its importance in post-MI remodeling, the specific targeting of periostin as a point of intervention in post-MI cardiac fibrosis is of great interest. A study using periostin-neutralizing antibodies in an in vivo rat MI model showed promising evidence that not only does post-MI infusion of anti-periostin antibodies reduce infarct size, but also improved cardiac fractional shortening and ejection fraction 8 weeks after MI [102]. It was specifically found that periostin exon 17 was the preferential target for reducing the effects of chronic post-MI fibrogenesis, confirming previous reports that periostin splice variants lacking exon 17 are beneficial in combatting cardiac remodeling [94]. The cumulative body of evidence supporting periostin's role in cardiac fibrosis and the ability to target it in vivo generates an auspicious vision for future animal models and potentially, clinical trials.

Non-mesenchymal effects of periostin—cardiac regeneration

While endogenous cardiac regeneration remains a contentious notion [10, 11], the myocardium remains unique in its response to injury. Current therapies used for the treatment of post-MI fibrosis and heart failure only serve to alleviate the symptoms, rather than ameliorating cardiac function; this is primarily due to the inability for human cardiomyocytes to readily regenerate after an acute insult.

One approach to mitigate the effects of sudden loss of cardiomyocytes is cardiac cell tissue regeneration by the exogenous expression of factors which promote re-entry into the cell cycle. Due to its ability to promote mesenchymal cell proliferation, periostin has been viewed as a potential point of intervention for post-MI cardiac regeneration. Work by Kuhn et al. demonstrated that in vitro treatment of rat cardiomyocytes with recombinant periostin promoted cell cycle re-entry and PI3K/Akt signaling [52]. The group also utilized a rat post-MI model of sudden cardiomyocyte loss to examine the capacity for recombinant periostin to regenerate infarcted tissue. Long-term, post-MI delivery of periostin via a bioresorbable ECM patch was shown to not only improve fractional shortening and ejection fraction, but also reduce the degree of replacement fibrosis incurred after infarction [52]. It should be noted, however, that the recombinant periostin implemented in these studies was truncated; this form was lacking the N-terminal signal peptide, as well as the alternatively spliced C-terminal region. It is important to recognize this alteration, as these data were later contested as another report indicated that periostin did not affect cardiomyocyte proliferation [69]. In a transgenic mouse model overexpressing full-length periostin via an inducible α-myosin heavy chain promoter, Lorts et al. determined that periostin did not induce cardiomyocyte proliferation in the post-MI heart. They also did not see any cell cycle activation in neonatal cardiomyocytes transduced with a periostin-expressing adenoviral vector. This is a stark contrast to recent transgenic studies which indicate that periostin ablation prevents neonatal cardiomyocyte regeneration, and inhibited PI3K signaling [19]. There are two experimental differences that may account for the disparate results: first, the transgenic mice constitutively overexpressed periostin, whereas previous studies only applied recombinant protein acutely; second, the transgenic mice overexpressed full-length periostin, which still contains the alternatively spliced region. To complicate the matter, further studies repeating the exogenous application of ECM-bound periostin into infarcted myocardium confirmed the results obtained by Kuhn et al., albeit to a lesser degree [53]. Again, discrepancies could be attributed to the fact that a porcine model of post-MI remodeling was used, rather than a murine one. Moreover, it was also found that the large animal model was distinguished by a marked increase in myocardial fibrosis 3 months post-treatment, compared to untreated controls [53]. While the various conditions in which periostin-mediated cardiac regeneration have been diverse and at times contradictory, further investigations into the effects of the different isoforms of periostin is warranted. Periostin may be necessary for cardiomyocyte renewal, but not sufficient on its own; rather, it is very possible that periostin is only required as an intermediary in cardiac regeneration. With this is mind, it is still important to consider periostin isoforms or mimetics as novel therapeutic tools in future clinical interventions for the treatment of post-MI hearts.

Future directions

As a central player in tissue response to mechanical stress and injury, periostin is a pleiotropic matricellular protein whose regulation is still relatively uncharacterized. With this in mind, several avenues of exploration hold potential answers to better understand transcriptional and translational modulation of periostin. First, as periostin expression responds to SMAD-dependent TGF-β/BMP stimulation, further investigations into endogenous repressors of the signaling cascade may provide further insight into its transcriptional regulation. The SKI/SNON family of proteins has been shown to not only inhibit SMAD2/3-inducible signaling [24], but also have the potential to attenuate cardiac myofibroblast activation [22, 23]. Similarly, the homeobox protein TGIF1 is also a SMAD2 transcriptional co-repressor which downregulates TGF-β signaling [87]; however, little is known about its function in cardiac tissues. Besides regulators of TGF-β, the relationship of periostin to the Hippo signaling pathway may also be a point of interest when considering the regulation of periostin. The activation of the

mitogenic Hippo nuclear effectors TAZ (transcriptional co-activator with a PDZ-binding domain; also known as WW domain-containing transcription regulator 1, or WWTR1) and YAP (Yes-associated protein; also known asYAP1), is characterized by multiple instances of potential crosstalk with periostin [68, 106]. Mechanosensory signaling cascades which activate WNT/β-Catenin signaling [2, 60, 118] and serum response factor (SRF) and are associated with cardiac fibrosis and expansion of the extracellular matrix [29, 77] and may have roles for both periostin and YAP/TAZ; however the existence of a shared regulatory relationship has yet to be explored.

The relationship between cells and their extracellular environment is of paramount importance when considering cardiovascular development and disease. The multifaceted nature of periostin and the specificity of its mesenchymal source within cardiovascular tissues are unique qualities which make it an attractive biomarker and potential therapeutic target. Given its relevance to both physiological and pathological expression of matrix components in the heart, continued experimentation toward elucidation of periostin's effects in cardiac extracellular matrix needs to be carried out, including those aimed at clinical translation.

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Compliance with ethical standards

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

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